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Health and Environmental Effects Profile for Acrylamide

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR ACRYLAMIDE

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PREFACE

The first draft of this document was prepared by Syracuse Research Corporation under Contract No. 68-03-3228. This document was subsequently reviewed and revised by ECAO-Cincinnati and the OHEA offices of CAG, EAG and REAG.

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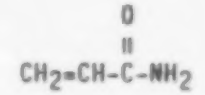
LIST OF ABBREVIATIONS

BOD	Biochemical oxygen demand
bw	Body weight
CAS	Chemical Abstract Service
CNS	Central Nervous System
DNA	Deoxyribonucleic acid
F	Potency factor
i.v.	Intravenous
i.p.	Intraperitoneal
K_{ow}	Log octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
MTD	Maximum Tolerated Dose
ppb	Parts per billion
ppm	Parts per million
SCE	Sister chromatid exchange
STEL	Short-term exposure level
TLC	Thin-layer chromatography
TPA	12-O-tetradecanoyl-phorbol-13-acetate
TWA-TLV	Time-weighted average-Threshold limit value

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The chemical commonly known as acrylamide is also known by the synonyms, propenamide and acrylic amide. The structure, molecular formula and molecular weight for acrylamide are as follows:



The molecular formula for acrylamide is C_3H_5NO and the molecular weight is 71.08. The CAS Registry number for acrylamide is 79-06-1.

1.2. CHEMICAL AND PHYSICAL PROPERTIES

Acrylamide is an odorless, white crystalline solid at room temperature (Hawley, 1981; Carpenter and Davis, 1957). Selected physical properties of this compound are listed below (MacWilliams, 1978; Carpenter and Davis, 1957, unless otherwise stated):

Melting point:	84.5°C
Boiling point:	87°C at 2 mm Hg 103°C at 5 mm Hg 125°C at 25 mm Hg
Density:	1.27 g/mL at 25°C
Vapor pressure:	0.007 mm Hg at 25°C
Water solubility:	2,155,000 mg/L at 30°C
Log K_{ow}:	-0.67 (Hansch and Leo, 1981)

Acrylamide is soluble in other polar solvents such as acetone, methanol and ethanol, and is almost insoluble in nonpolar solvents such as heptane and carbon tetrachloride (Carpenter and Davis, 1957).

Acrylamide undergoes Michael-type addition reactions called carbamylethylations with ammonia, amines, alcohols, etc. It also reacts with formaldehyde under basic conditions to give methylol acrylamide, and with sodium hypochloride to give N-chloroacrylamide. Acrylamide functions as a dienophile in Diel-Alder reactions (Carpenter and Davis, 1957).

The most important reactions of acrylamide are its polymerization reactions. The polymerization reaction is initiated by many free-radical sources, such as ionizing radicals, sodium persulfate and sodium bisulfite. Depending on reaction conditions, both linear and cross-linked polymers can be obtained. (MacWilliams, 1978; Davis et al., 1976).

1.3. PRODUCTION DATA

Current commercial methods for the production of acrylamide are based on hydration of acrylonitrile by different routes. In one method, acrylonitrile is hydrated with sulfuric acid monohydrate according to the following reaction:

$$CH_2{=}CHCN + H_2SO_4{\cdot}H_2O \rightarrow CH_2{=}CHCONH_2{\cdot}H_2SO_4$$

The above reaction is usually run in the presence of $CuSO_4$ to inhibit side reactions. The product formed by this reaction is neutralized by the addition of either ammonia or lime. The ammonium sulfate or calcium sulfate formed is removed from acrylamide by crystallization. The crude acrylamide is then purified either by recrystallization, vacuum sublimation, or ion exclusion (MacWilliams, 1978).

In the second commonly used commercial method, the hydration of acrylamide is performed in the presence of a catalyst according to the following reaction:

$$CH_2{=}CHCN + H_2O \xrightarrow{\text{catalyst}} CH_2{=}CHCONH_2$$

This process eliminates the by-product sulfate formation. Although several catalysts have been used, all commercial processes use a copper based catalyst for the hydration reaction (MacWilliams, 1978).

According to SRI (1984), the following three United States companies are the manufacturers of acrylamide as of January, 1984:

Company and Location	Production Capacity (millions of pounds/year)
American Cyanamid, Avondale, LA Linden, NJ	100
Dow Chemical U.S.A., Midland, MI	100
Nalco Chemical Co., Garyville, LA	15
Total	215

The Nalco production facility in Garyville, LA manufactures polyacrylamide without isolating the crude monomer (SRI, 1984). The USITC (1984), however, lists Sohio Chemical Co., Lima, OH and another confidential manufacturer as the United States manufacturers of acrylamide in 1983, in addition to Dow Chemical Co. and American Cyanamid Co. In 1983, the United States production of acrylamide was 86.2 million pounds. Only ~31.9 million pounds of the total production volume in 1983 was sold to the merchant market (USITC, 1984).

1.4. USE DATA

The primary use of acrylamide is in the production of polymers and copolymers. The largest market for polyacrylamide is in sewage and wastewater treatment plants, where it is used as a flocculant. Polyacrylamide is also used for treatment of potable water as a coagulant aid. The amount of residual monomer allowed in such application is 0.05%. The paper and pulp industry is the second largest user of polyacrylamide. In this application,

polyacrylamide strengthens and improves the quality of paper and paperboard products. The residual acrylamide content of paper and paperboard for food contact usage is regulated by the FDA. Water soluble polyacrylamide is also used as an additive for enhanced oil recovery in the petroleum industry (Davis et al., 1976).

Acrylamide monomer is used in the production of chemical grouts and soil stabilizers for use in the construction of dams, foundations, tunnels and roadways. Small quantities of acrylamide are used in resins for promoting adhesion and other properties. In combination with certain dyes, acrylamide is also used in photographic applications. Acrylamide has been used in the textile industry to impart certain desirable characteristics to fabrics (Davis et al., 1976; MacWilliams, 1978).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

Relatively little is known about the fate of acrylamide in aquatic media. The fate of acrylamide with respect to its biodegradation potential in aquatic media has received more attention than any other degradative pathway.

Several investigators have shown that isolated microorganisms can biodegrade acrylamide by using acrylamide as a sole source of carbon and nitrogen, or as a sole source of carbon or nitrogen. The isolated microorganisms capable of biodegrading acrylamide include a species of Arthrobacter (Yamada et al., 1979; Asano et al., 1982), Norcardia rhodochrous species (Digeronimo and Antoine, 1976; Hynes and Pateman, 1970), Bacillus sphaericus and Pseudomonas putrefaciens species (Maekawa and Shinpo, 1977) and species of Rhodococcus (Arai et al., 1981; Collins and Knowles, 1983).

The biodegradation potential of acrylamide with sewage seed as microbial inoculum was reported by Bridie et al. (1979a). In a 5-day BOD test with nonadapted seed, only 4% degradation of acrylamide was observed; however, the biodegradation rose to 69% when adapted seed was used. The need for acclimatized microorganisms for faster biodegradation of acrylamide was also noted by Cherry et al. (1956). These authors incubated acrylonitrile in a natural river water and measured the COD and BOD at periodic intervals as a measure of degradation of acrylamide. The degradation of acrylamide at a concentration of 10-20 ppm was complete in ~12 days with nonacclimated microorganisms in the river water. When the microorganisms were acclimated for 33 days (by redosing of sample medium), the complete degradation of

acrylamide took only 2 days. Cherry et al. (1956) also observed that the degradation was ~5 times slower with a seed material acclimated to acrylonitrile than seed acclimated to acrylamide.

The biodegradability of acrylamide with activated sludge as microbial inoculum was also reported by Kitano (1978), who observed ~73% degradation (measured as BOD) after 2 weeks of incubation with a 100 ppm acrylamide solution.

It can be concluded from the preceding discussions that acrylamide is biodegradable in aquatic media. The biodegradation of acrylamide in aqueous media was also confirmed by the MITI test in Japan (Kawasaki, 1980); that biodegradation is faster with acclimated microorganisms was noted by Thom and Agg (1975).

The biodegradation of acrylamide in natural and polluted water was studied by Brown et al. (1980a). In natural river water, the complete degradation of acrylamide took 4-5 days. The complete degradation of acrylamide in seawater, estuarine water, sewage water and industrial effluents took between 4 and 30 days. No degradation of acrylamide in tap water was observed in 2000 hours. These authors suggested that the dominant cause of acrylamide loss in aquatic media is microbial degradation, and that the biodegradation is temperature dependent, with the degradation slower at temperatures less than the ambient temperatures of 20$\pm$5°C.

The degradation of acrylamide in natural river water and in sewage effluent was studied by Croll et al. (1974). These authors reported a 50-hour lag period before the commencement of biodegradation in natural river water. The degradation was, however, complete in 200 hours. When the same river water was inoculated with microorganisms capable of degrading acrylamide, the lag period was reduced to 5 hours and the degradation of

acrylamide was complete in 40 hours. With settled sewage effluent as inoculum, the complete degradation of acrylamide took ~16 days in aerated vessels and 9 days in closed vessels.

The biodegradability of acrylamide by activated sludge and percolating biological filter used during sewage treatment was studied both in laboratory experiments and in in situ experiments by exposing an activated sludge and a percolating biological filter plant to constant dosings of acrylamide (Brown et al., 1982). About 50-70% of acrylamide biodegraded in 24-48 hours in the in situ experiments. In laboratory experiments, 100% loss of acrylamide was recorded in 24 hours. Similar in situ and laboratory experiments were performed with river water. The in situ experiments indicated no loss of acrylamide in 4-5 hours and possibly up to several days, although some increase in microbial degradation was noted with the acclimatization of microorganisms in the river water. The laboratory experiments with river water indicated no loss of acrylamide in 2 days. The complete loss of acrylamide occured in 4-83 days, depending on the temperature of the water and the type of discharged pollutant present in the collected water.

Brown et al. (1982) also dosed tap water with acrylamide and incubated the water with varying quantities of activated sludge. While an increased rate of acrylamide loss was noted as the dose of activated sludge was increased, no loss occurred for the tap water in 24 hours without the activated sludge inoculum.

Information regarding the degradation of acrylamide in aquatic media by such chemical processes as hydrolysis, oxidation and photolysis have not been studied comprehensively. The hydrolysis of acrylamide at both high and low pHs was reported by Davis et al. (1976). At a pH of 12 and a tempera-

ture of 51°C, only ~7% of acrylamide hydrolyzed in ~16 hours. The hydrolysis rate was 0.9%/hour at a pH of 8 and a temperature of 50°C. Pertinent data regarding the hydrolysis rate of acrylamide at environmentally significant temperature and pH were not located in the available literature cited in the Appendix. It appears, however, that hydrolysis may not be a significant fate of acrylamide in aquatic media.

Acrylamide in aqueous solution absorbs light in the range from 200-280 nm (Davis et al., 1976). Therefore, it is unlikely that photolysis will be a significant fate process for acrylamide in aquatic media. The rate constant for the oxidation of acrylamide by OH radicals is ~1.9-3.3x10^{9} $M^{-1}s^{-1}$ (Anbar and Neta, 1967; Dorfman and Adams, 1973). If the concentration of OH radicals in natural surface water is assumed to be 10^{-17}M, the half-life of acrylamide that is due to OH radical reaction is ~1 year. Therefore, this oxidation reaction may not be a significant fate determining process for this chemical in aquatic media.

The reaction of Cl_2 and O_3 with acrylamide in aqueous solution is significant in determining the fate of this chemical during water treatment processes. At an acrylamide concentration of 6 ppb and water pH of 7, 3 ppm O_3 at a contact time of 0.5 hours removed 100% of the compound. The removal rate was much slower with Cl_2. When the Cl_2 concentration was 10 ppm, 64% of acrylamide was removed from the water at a pH of 5 and a contact time of 4 hours. When the water pH was 8.5, no acrylamide was removed from the water at a contact time of 5 hours (Croll et al., 1974).

The removal of acrylamide from aqueous media through physical mechanisms such as volatilization and sedimentation has not been studied comprehensively. Davis et al. (1976) speculated that evaporation of acrylamide from aquatic media would be insignificant. This conclusion can be supported by

considering the Henry's law constant (H) (~10^{-10} atm•$m^3$$mole^{-1}$) and the volatility characteristic associated with various H values as given by Lyman et al. (1982).

The possibility of removal of acrylamide through sediment adsorption in natural water was determined experimentally by Brown et al. (1980a,b, 1982). It was concluded that no significant sedimentation of acrylamide occurs in natural water or during treatment of sewage containing acrylamide. Experiental data regarding bioaccumulation and biomagnification of acrylamide in aquatic media were not located in the available literature cited in the Appendix. Based on the log K_{ow} value of -0.67, it is likely that this compound will not bioaccumulate in aquatic organisms.

2.2. AIR

Pertinent data regarding the fate of acrylamide in the atmosphere were not located in the literature cited in the Appendix. This is not surprising in view of the fact that no acrylamide has ever been detected in the atmosphere, even near manufacturing and user sites (Section 3.2.). The low chemical reactivity of this compound in the aquatic media, however, predicts that the compound, if present in air, will be persistent in this medium. Because of its high water solubility, the physical removal of acrylamide through wet precipitation may be significant.

2.3. SOIL

The fate of acrylamide in soil was studied by several investigators. In moist soil, an enzyme (acrylamide amidohydrolase) hydrolyzes acrylamide to acrylic acid and ammonia or ammonium ions. In aerobic soils, the NH_4^+ ions are converted to NO_3^- or NO_2^-. In waterlogged soil where anaerobic conditions exist, acrylamide is hydrolyzed to NH_3 and NH_4^+ ions and are not further oxidized to NO_2^- and NO_3^-. After 7 days of

aerobic incubation at 30°C, depending upon the type of soil, 35-84% of the acrylamide degraded to inorganic N-compounds. The degradation of acrylamide under the same conditions after 14 days of incubation ranged from 74-94% depending upon the nature of soil. In waterlogged soil, incubation at 20°C resulted in the degradation of 18-84% acrylamide in 7 days and 64-89% in 14 days (Abdelmagid and Tabatabai, 1982; Frankenberger and Tabatabai, 1982).

The degradation of acrylamide in soil was also studied by Lande et al. (1979). These authors estimated that the upper limit for the metabolic half-life of acrylamide in soil at ambient temperature varied from 21 hours in a loam soil (2.8% organic matter) to 36 hours in a loamy sand soil (3.9% organic matter). The half-life was found to be influenced by incubation temperature, acrylamide concentration and the season of sample collection. For example, a silt loam soil (8.3% organic matter) incubated at 22°C, had estimated half-lives of 45 hours and 18 hours when the soil was collected in the spring and summer, respectively. The same silt loam soil had estimated half-lives of 96 hours and 10 hours at incubation temperatures of 10°C and 37°C, respectively. The effect of initial acrylamide concentration was shown by the increase of estimated half-life from 18-95 hours when the acrylamide concentration in the same soil was increased from 25-500 ppm. When the acrylamide was incubated in anaerobically maintained soil, only ~20-55% of the compound degraded in 336 hours.

That the first step in the degradation of acrylamide in soil is the hydrolytic production of acrylic acid and NH_4^+ ions was also established by Nishikawa et al. (1979). These authors also reported that the acrylic acid formed in the soil was completely degraded in 15 days.

Lande et al. (1979) evaluated the R_f values of acrylamide by soil TLC experiments in the range of 0.64-0.88. Therefore, acrylamide is probably

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16. ABSTRACT

The Health and Environmental Effects Profile for acrylamide was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Acrylamide has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for acrylamide is 2.3 $(mg/kg/day)^{-1}$ for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for acrylamide is 100.

17. KEY WORDS AND DOCUMENT ANALYSIS		
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leachable in soil. The mobility of acrylamide in soil is expected because of its poor sorption onto various clay and peat samples (Brown et al., 1980a,b) and its high solubility in water. The high mobility of acrylamide in soil does not guarantee the leaching of acrylamide in groundwater because of its reasonable rate of biodegradability. In cases where the biodegradability is retarded because of a high concentration of acrylamide, as in the case of an accidental spill or disposal in a dump site, some leaching of acrylamide is expected.

The translocation of acrylamide from soil to leaves and stems in rice seedlings and Chinese cabbage was observed by Nishikawa et al. (1979) and Nishikawa et al. (1978); however, the amount of translocated acrylamide in leaves and stems gradually decreased with time (Nishikawa et al., 1978).

3. EXPOSURE

3.1. WATER

Although acrylamide could contaminate aquatic media during its production, transport, storage, use and disposal (Davis et al., 1976) of monomer/polymer, few monitoring data are available. The level of acrylamide monitored in a few industrial effluents is presented in Table 3-1. When clay pit effluent (Table 3-1) was discharged into a receiving stream, the concentration of acrylamide was reduced to 1.2 µg/ℓ. It was further diluted to 0.3 µg/ℓ downstream at the water intake point of a British waterworks (Croll et al., 1974). Brown et al. (1980c) failed to detect (detection limit of 0.2 µg/ℓ) any acrylamide as a result of treatment of potable water with the recommended dose of polyacrylamide. The average dose of polymer added to water does not exceed 0.5 mg/ℓ with the maximum not exceeding 1 mg/ℓ (Croll et al., 1974). The effect of overdosing of polymer was studied by Brown et al. (1980c). At a dose 100 times higher than the recommended dose, Brown et al. (1980c) detected up to 8.6 µg/ℓ of acrylamide in potable water.

3.2. AIR

Only one study pertaining to the level of acrylamide in ambient air was located in the literature cited in the Appendix. No acrylamide was detected (detection limit of 0.1-1 µg/m³) in either the vapor or particulate phase of the air around five United States producer and user sites of acrylamide/polyacrylamide (Going, 1978).

3.3. FOOD AND OTHER INGESTED MATERIALS

Pertinent data regarding the level of acrylamide in food or other ingested materials were not located in the available literature cited in the Appendix.

TABLE 3-1

Acrylamide Levels in Some Industrial Effluents

Effluent	Concentration (µg/ℓ)	Reference
Colliery tailings lagoon	39-42	Croll et al., 1974
Coal washing effluent lagoon	1.8	Croll et al., 1974
Colliery/coking plant effluent	0.74	Croll et al., 1974
Paper mill treated effluent	0.47-1.2	Croll et al., 1974
Clay pit effluent	16	Croll et al., 1974
Crude sewage for a user industry	1.1	Croll et al., 1974
Above after treatment	0.28	Croll et al., 1974
Paper mill untreated effluent	ND[a]-45.4	Brown et al., 1980c
Paper mill treated effluent	ND[a]-14.4	Brown et al., 1980c
China clay industry effluent	ND[a]	Brown et al., 1980c
Acrylamide/polyacrylamide production effluent	ND[b]-1500	Going, 1978
Polyacrylamide user effluent	ND[b]	Going, 1978

[a]ND = Not detected, the detection limit being 0.2-1 µg/ℓ

[b]The detection limit was 0.8 µg/ℓ.

3.4. DERMAL

Although fatal intoxication has been reported following industrial exposure (Davis et al., 1976), no quantitative data regarding dermal exposure to acrylamide under occupational conditions were located in the literature cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Absorption of acrylamide across the gastrointestinal tract can be inferred from the reports of Miller et al. (1982) and Dixit et al. (1982), (Sections 4.3. and 4.4.). A review by Tilson (1981) reported that neurotoxic effects were observed after acrylamide was administered dermally and orally, indicating that the chemical was absorbed by these routes.

4.2. DISTRIBUTION

A single dose of 100 mg/kg of [1-^{14}C]-acrylamide was administered by the tail vein to three male albino rats (Hashimoto and Aldridge, 1970). The levels of radioactivity in the blood, liver, kidney and nervous tissue are reported in Table 4-1. Although the level of radioactivity decreased with time, there was a considerable amount of radioactivity present 14 days after a single i.v. dose (Table 4-1). The high level of radioactivity in the blood was associated with the red blood cell fraction and not the plasma; Hashimoto and Aldridge (1970) suggested that acrylamide may react with rat hemoglobin.

Male Fischer 344 rats were treated intravenously with a single dose of 10 mg/kg of [2,3-^{14}C]-acrylamide (Miller et al., 1982). Tissue distribution of radiolabel was determined in the muscle, skin, fat, testes, liver, kidney, small intestine, lung, brain, spinal cord and sciatic nerve during a period of 7 days after dosing. Immediately after dosing, 48, 15, 12 and 7% of the radioactivity recovered from the body tissue was located in the muscle, skin, blood and liver, respectively. Although a small percentage of radioactivity remained in the tissues for weeks, Miller et al. (1982) concluded that acrylamide or its metabolites were not selectively concentrated in the nervous tissue.

TABLE 4-1

Distribution of [^{14}C] in Tissues After a Single Intravenous Dose of [1-^{14}C]-Acrylamide*

Time after Administration	Tissue	Homogenate	*Free and Soluble*	Protein Bound
		(nmol/g original tissue)		
Acrylamide (100 mg/kg bw)				
24 hours	blood	1280	160	938
	plasma	63	0.0	NR
	brain	262	105	156
	spinal cord	175	44	110
	sciatic nerve	149	60	NR
	liver	368	70	323
	kidney	508	195	280
4 days	blood	1360	7.4	920
	plasma	26	0.0	NR
	brain	151	20	95
	spinal cord	131	19	89
	sciatic nerve	100	16	89
	liver	142	20	158
	kidney	248	66	181
14 days	blood	772	1.8	920
	plasma	6.0	0.0	NR
	brain	72	3.3	49
	spinal cord	71	2.8	44
	sciatic nerve	57	0.0	NR
	liver	57	1.6	61
	kidney	91	1.2	76

*Source: Hashimoto and Aldridge, 1970

Intravenous administration of 100 mg/kg of [1-^{14}C]-acrylamide to male rats resulted in distribution of [1-^{14}C]-acrylamide throughout total body water within a few minutes (Edwards, 1975). The highest concentration of [1-^{14}C]-acrylamide in the blood (3.2 nmol/mL), reached almost immediately after dosing, decreased exponentially. [1-^{14}C]-Acrylamide had a half-life of 1.9 hours in the blood.

As reviewed by U.S. EPA (1980), the distal half of the sciatic nerve in mice accumulated 2.4 times as much label as the proximal half after the administration of radioactive acrylamide (Ando and Hashimoto, 1972).

A study of Ikeda et al. (1983) indicated that acrylamide crossed the placenta in rats, rabbits, beagle dogs and miniature pigs when administered intravenously late in gestation, and that the fetal distribution of acrylamide was uniform.

4.3. METABOLISM

Following treatment of rats by an unspecified route with 0.5-50 mg/kg of ^{14}C-acrylamide (position of label not specified), the urine contained 4% of the administered radioactivity as parent compound, 34 and 5% as two glutathione conjugates and 16% as unknown metabolite (Pastoor, 1982). The two glutathione conjugates and the unknown metabolite were detected in the urine up to 20-24 hours after dosing. Unmetabolized radioactive acrylamide was detected in the urine up to 8 hours after dosing (Pastoor, 1982).

At least four metabolites were identified in the urine of rats treated orally with a single dose of 100 mg/kg of [2,3-^{14}C]-acrylamide (Miller et al., 1982). N-Acetyl-S-(3-amino-3-oxypropyl)cysteine was identified in the urine by means of TLC and accounted for ~48% of the administered dose.

Three other metabolites were found, but not identified, by Miller et al. (1982). Miller et al. (1982) concluded that the major route of acrylamide metabolism involves glutathione conjugation.

Liver glutathione concentration decreased rapidly to ~36% of its normal value 2-4 hours after i.v. dosing of rats with [1-^{14}C]-acrylamide. Within 24 hours after dosing, however, liver glutathione levels were within normal range (Edwards, 1975).

The urine of adult male rats treated by gavage with a single dose of 0, 25, 50 or 100 mg/kg of acrylamide was collected for 24 hours after dosing (Dixit et al., 1982). Two thioether compounds, mercapturic acid and cysteine-S-propionamide, were identified by TLC in the urine of treated rats. Of the administered dose, ~7% was identified as urinary mercapturic acid. Dixit et al. (1982) reported that the conjugation of acrylamide with glutathione occurs both enzymatically and nonenzymatically. The conjugation of acrylamide and glutathione is catalyzed enzymatically by liver and brain glutathione-S-transferases.

4.4. EXCRETION

A single dose of 100 mg/kg of [1-^{14}C]-acrylamide was administered by the tail vein to two male albino rats (Hashimoto and Aldridge, 1970). Although a total of 60% of the administered radioactivity was excreted in the urine within 3 days of dosing, 40% of the administered radioactivity was excreted in the urine within 1 day of dosing. Within 8 hours of dosing, 6% of the administered radioactivity was exhaled as $^{14}CO_2$. Small amounts of $^{14}CO_2$ continued to be exhaled, but most of the $^{14}CO_2$ exhaled after [1-^{14}C]-acrylamide administration was detected within the first 8 hours after dosing (Hashimoto and Aldridge, 1970).

Bile duct-cannulated rats were given 100 mg/kg of [1-^{14}C]-acrylamide intravenously and excreted glutathione-conjugated acrylamide rapidly in the bile (Edwards, 1975).

Male Fischer 344 rats were treated orally with a single 1.0, 10 or 100 mg/kg dose of [2,3-^{14}C]-acrylamide (Miller et al., 1982). Between 53 and 67% of the administered radioactivity was excreted in the urine and feces within 24 hours, regardless of the administered dose. Of the administered dose, ~71% had been excreted in the urine and 6% in the feces within 7 days of dosing. Enterohepatic circulation may be involved in the disposition of [2,3-^{14}C]-acrylamide, since 15% of the administered dose appeared in the bile within 6 hours of dosing. No radioactivity was detected in expired air. A total of ~90% of the administered radioactivity was recovered from the tissues, body fluids, urine and feces (including intestinal contents) of the rats treated orally with [2,3-^{14}C]-acrylamide. More than 90% of the recovered radioactivity had been detected in the urine (Miller et al., 1982).

5. EFFECTS

5.1. CARCINOGENICITY

Groups of 90 male and 90 female CDF Fischer 344 rats were treated with 0, 0.01, 0.1, 0.5 or 2.0 mg/kg/day of acrylamide in their drinking water for 738-746 days (Dow, 1984). A statistically significant increase in the incidence of mammary tumors, CNS tumors, thyroid follicular tumors, and uterine adenocarcinoma were reported in female rats (Table 5-1). A statistically significant increase in the incidence of thyroid follicular tumors and scrotal mesotheliomas was reported in the male rats (Table 5-1). Because the incidence range in historic control 24-month-old female Fischer 344 rats for pituitary gland adenomas and adenocarcinomas was reported to be 18-70% (mean, 44%) and 0-19% (mean, 3.5%), respectively (NTP, 1983), the increased incidence of pituitary adenomas in females was not considered to be biologically significant (Dow, 1984). Similarly, because the incidence range in the 24-month-old male Fischer 344 rat for adrenal medullar pheochromocytomas was reported to be 17% (Solleveld et al., 1984), the increased incidence of adrenal medullar pheochromocytomas was not considered to be biologically significant (Dow, 1984). A review of the data for these two tumor types indicates that, when benign and malignant tumors of these types are combined, a statistically significant increase in exposed animals is no longer evident. For this reason, the incidence rates of these tumor types are not considered biologically significant for the purposes of this assessment. The exposed animals showed no increase in incidence or a lower incidence for the malignant forms. There was a statistically significant increase in the number of adenomas and/or adenocarcinomas of the clitoris in the female rats, but only $\leq$5 rats were examined from each group and, therefore, although there is some qualitative evidence that acrylamide causes clitoral tumors, the quantitative evidence is very limited (Table 5-2).

TABLE 5-1

Carcinogenicity of Acrylamide in Orally Exposed Fischer 344 Rats[a,b]

Sex	Dose (mg/kg/day)	Target Organ	Tumor Type	Tumor Incidence
F	0	mammary gland	adenoma/fibroma/	10/60
	0.01		adenofibroma	11/60
	0.1			9/60
	0.5			19/58
	2.0			23/61[c,d]
F	0	CNS	glioma/	1/60
	0.01		astrocytoma	2/60
	0.1		oligodendroglioma	1/60
	0.5			1/60
	2.0			9/61[d]
F	0	thyroid gland	follicular cell	1/58
	0.01		adenoma/	0/59
	0.1		adenocarcinoma	1/59
	0.5			1/58
	2.0			5/60[c]
F	0	uterus	adenocarcinoma	1/60
	0.01			2/60
	0.1			1/60
	0.5			0/59
	2.0			5/60[c]
M	0	scrotum	mesothelioma	3/60
	0.01			0/60
	0.1			7/60
	0.5			11/60[c]
	2.0			10/60[c]
M	0	thyroid gland	adenoma	1/60
	0.01			0/58
	0.1			2/59
	0.5			1/59
	2.0			7/59[c,d]

TABLE 5-1 (cont.)

Sex	Dose (mg/kg/day)	Target Organ	Tumor Type	Tumor Incidence
		QUALITY OF EVIDENCE		
Strengths of Study:		Several dose levels were used; the highest dose was predetermined to be the MTD, based on microscopically but not clinically detected peripheral neuropathy; an adequate number of rats in each treatment group as well as an adequate number of rats evaluated for each target organ; duration of treatment covered life-span of animals; both sexes were treated; comprehensive histologic examination was performed.		
Weakness of Study:		Only one species was studied.		
Overall Adequacy:		Adequate		

[a]The vehicle was drinking water and the purity of compound was 96-99% in all studies.

[b]Duration was 738-746 days.

[c]There was a statistically significant increase compared with controls after a mortality adjustment had been made using the Mantel-Haenzel Procedure (p=0.05).

[d]Statistically significant increase at the 2.0 mg/kg/day dose by Fisher Exact Test (p=0.05) performed by Dow, 1984.

TABLE 5-2

Incidence of Adenoma and/or Adenocarcinoma of the Clitoral Gland in Female Fischer 344 Rats After Exposure to Acrylamide for 2 Years[a]

	Acrylamide (mg/kg/day)				
	0	0.01	0.1	0.5	2.0
Total number of rats examined	2	3	4	4	5
Number of rats with adenocarcinoma	0	0	0	2	0
Number of rats with adenoma	0	1	3	2	5[b]

[a]Source: Dow, 1984

[b]There was a statistically significant increase compared with controls after a mortality adjustment using the Mentel-Haenzel procedure (p=0.05).

Similarly, although there is some qualitative evidence that acrylamide exposure may be correlated with an increased incidence of squamous papillomas on the tongue, hard palate and lips of female rats (Table 5-3), the quantitative evidence is limited.

There was a time-dependent increase in the incidence of mammary adenocarcinoma regardless of acrylamide treatment. Although the incidence of each benign mammary tumor type considered separately was not significantly affected by acrylamide, when considered collectively there was a statistically significant increase in the incidence of adenoma, fibroma and fibroadenoma in female rats treated with 2.0 mg/kg/day of acrylamide for 2 years (see Table 5-1). Similarly, the incidence of either astrocytoma or glial cell tumors considered separately in the female CNS was not significantly affected by acrylamide treatment. When the incidences of these two tumor types are combined, however, there is a statistically significant increase in the combined incidence of CNS tumors in female rats treated at 2.0 mg/kg/day as indicated in Table 5-1. As in the mammary gland and CNS, a statistically significant increase in the incidence of thyroid tumors in female rats was obtained only after combining the incidence of adenocarcinoma and papillary adenoma (see Table 5-1). As indicated in Table 5-1, the increased incidence of adenocarcinoma in the uterus was statistically significant in the rats treated with 2 mg/kg/day of acrylamide.

In the male rats, a statistically significant increase in thyroid adenomas was observed only in rats treated with 2 mg/kg/day of acrylamide. The increased incidence of scrotal mesothelioma, however, was statistically significant in male rats treated with 2.0 and 0.5 mg/kg/day of acrylamide, as indicated in Table 5-1. In addition, although not statistically significant, there appears to be an increased incidence of scrotal mesothelioma in rats treated with 0.1 mg/kg/day of acrylamide.

TABLE 5-3

Incidence of Squamous Papillomas From Tongue, Hard Palate or Lips in Female Fischer 344 Rats After Exposure to Acrylamide for 2 Years[a]

	Acrylamide Dose (mg/kg/day)				
	0	0.01	0.1	0.5	2.0
Tongue:					
Total number of rats examined	60	60	60	60	61
Number of rats with squamous papillomas	0	0	0	0	2
Hard palate and lip:					
Total number of rats examined	9	12	15	9	15
Number of rats with squamous papillomas	0	3	2	1	5[b,c]

[a]Source: Dow, 1984

[b]There was a significant increase compared with controls after the mortality adjustment by the Mentel-Haenzel procedure (p=0.05) was used.

[c]Because of the discrepancy in the number of rats examined for the incidence of squamous papillomas on the tongue and hard palate and lip, a combined incidence cannot be obtained by simple addition.

Because of the wide variety of tumors found in acrylamide treated rats, the incidence of malignant tumors from all sites is included in Table 5-1 for males and for females. Although the incidence data were reported by Dow (1984), statistical analysis performed at SRC (1985) using the Fisher's Exact test indicated that there was a statistically significant increase in the incidence of malignant tumors from all sites in both male and female rats that had been treated with acrylamide in the drinking water for 2 years. There was no statistically significant effect of acrylamide on the incidence of benign tumors from all sites in either male or female rats.

In a series of experiments, Bull et al. (1984a,b) tested acrylamide as tumor initiator and as a whole carcinogen in different strains of mice using various routes of administration. In an initiation-promotion assay, groups of 40, 6- to 8-week-old female Sencar mice were treated by gavage, intraperitoneally or topically on the dorsal shaved skin, with 0, 12.5, 25.0 or 50.0 mg/kg/application of acrylamide for a total of six applications and total doses of 0, 75, 150 or 300 mg/kg, respectively, over a 2-week period (Bull et al., 1984a). After a 2-week rest period, 1.0 µg o-tetradecanylphorbol-13-acetate (TPA, a tumor promoter) in 0.2 mL of acetone was applied to the shaved back of each mouse 3 times/week for 20 weeks. The animals were observed weekly and at the termination of the study, 52 weeks after the initial acrylamide treatment. No signs of peripheral neuropathy were observed with the described treatment schedule. An increased incidence of squamous cell papilloma and squamous cell carcinoma of the skin was observed in mice treated with acrylamide and TPA by all three routes of exposure. Acrylamide treatment alone, however, did not result in an increased incidence of skin tumors. The incidence and histological classification of skin tumors from animals that died during the experiment or were

terminated at 52 weeks are summarized in Table 5-4. Some of the skin tumors regressed before the termination of the experiment and they are not included in Table 5-4. In addition to the increased incidence of skin tumors, there was a significant decrease in the time of appearance of the first tumor after acrylamide was given as an inducer in any of the three routes tested (Bull et al., 1984a).

Groups of 40 male and 40 female 8-week-old A/J mice were treated orally with 0, 6.25, 12.5 or 25 mg/kg/day of acrylamide 3 days/week for 8 weeks (Bull et al., 1984a). The mice were killed 7 months after the first acrylamide treatment. A significant dose-related increase in the number of pulmonary adenomas per mouse for both the males and the females was reported, but the data were not tabulated (Bull et al., 1984a). In another experiment, groups of 16 male and 16 female 8-week-old A/J mice were treated intraperitoneally with 0, 1, 3, 10, 30 or 60 mg/kg/day of acrylamide 3 days/week for 8 weeks (Bull et al., 1984a). The mice receiving the 60 mg/kg/day dose developed signs of neurotoxicity and were terminated. The remaining mice were killed 6 months after the first acrylamide treatment. The results of the experiment, summarized in Table 5-5, indicate that there was a significant ($p<0.01$) dose-related increase in the number of lung tumors/mouse as well as the number of mice with lung tumors. Bull et al. (1984a) reported that A/J mice usually develop between one and two lung tumors/animal by 1.5 years of age (Shimkin and Stoner, 1975; Stoner and Shimkin, 1982). Since this number was attained in treated animals at a younger age, acrylamide appeared to accelerate lung tumorigenesis.

Groups of 40 female Swiss-ICR mice were treated by gavage with 0, 12.5, 25 or 50 mg/kg/day of acrylamide 3 days/week for ? weeks (Bull et al., 1984b). After a 2-week rest period, 2.5 μg TPA, a tumor promotor, was

TABLE 5-4

Tumor-bearing Animals and Classification of Histologically Examined Skin Tumors in Sencar Mice Initiated with Acrylamide by Various Routes[a]

Total Dose (mg/kg)	Route of Administration	TPA	Cumulative No. of Tumor-Bearing Animals[b]/ No. of Animals Initiated	No. of Squamous Cell Papillomas/ No. of Animals Examined	No. of Squamous Cell Carcinomas/ No. of Animals Examined	Percent of Animals Bearing Squamous Cell Carcinomas
0[d]	p.o.	+	2/40	0/34	0/34	0
75	p.o.	+	12/40	3/35	2/35	5.7
150	p.o.	+	23/40	8/33	7/33	21.2
300	p.o.	+	30/40	11/38	6/38	15.8
300	p.o.	-	0/20	0/17	0/17	0
0[c]	i.p.	+	0/40	0/35	0/35	0
75	i.p.	+	10/40	2/38	2/38	5.2
150	i.p.	+	13/40	3/36	4/36	11.1
300	i.p.	+	21/40	6/35	4/35	11.4
300	i.p.	-	0/20	0/17	0/17	0
0	topical	+	7/40	5/36	0/36	0
75	topical	+	4/40	3/38	1/38	2.6
150	topical	+	11/40	3/35	2/35	5.7
300	topical	+	18/40	2/34	3/34	8.8
300	topical	-	0/20	0/20	0/20	0

[a]Source: Bull et al., 1984a

[b]To be included in the cumulative count, the animal must have had a lesion, 1 mm in diameter, for 3 consecutive weekly observations.

[c]Distilled deionized water was administered in the same volume (0.2 mL/mouse) and frequency as used in experimental groups.

[d]Ethanol was administered topically in the same volume (0.2 mL/mouse) and frequency as used for experimental groups.

TABLE 5-5

Effects of Acrylamide Administered Intraperitoneally on Development of Lung Tumors in A/J Mice[a]

Treatment	Sex	No. of Survivors/ Initial No. of Mice	Percent of Mice with Lung Tumor	Average No. of Lung Tumors/Mouse
None	M	16/16	31	0.31±0.48[b]
	F	14/16	50	0.50±0.52
	M, F	30/32	40	0.40±0.50
Distilled H_2O	M	16/16	13	0.06±0.25
	F	15/16	8	0.13±0.35
	M, F	31/32	10	0.10±0.30
Acrylamide				
1 mg/kg/day[c]	M	16/16	50	0.75±0.93
	F	17/17	35	0.35±0.93
	M, F	33/33	42	0.55±0.78
3 mg/kg/day[c]	M	16/16	38	0.69±1.03
	F	17/17	53	0.88±1.11
	M, F	33/33	46	0.79±1.05
10 mg/kg/day[c]	M	17/17	59	0.88±0.99
	F	14/15	79	1.57±1.79
	M, F	31/32	68	1.19±1.40
30 mg/kg/day[c]	M	15/16	93	1.87±1.55
	F	15/16	93	2.53±1.46
	M, F	30/32	93	2.20±1.52

[a]Source: Bull et al., 1984a

[b]Mean ± S.D.

[c]Given 3 days/week for 8 weeks

applied to the shaved back of each mouse for a period of 20 weeks. One group of 40 female Swiss-ICR mice were treated with 50 mg/kg/day of acrylamide by gavage 3 days/week for 2 weeks, but no promotor was applied 3 times weekly to the skin. The mice were observed for 52 weeks, at which time they were terminated. Treatment with acrylamide, followed by TPA promotion, resulted in a dose-related increase in squamous cell carcinomas; however, acrylamide treatment alone resulted in squamous cell carcinoma in only one mouse that had been treated with the highest dose of acrylamide. Acrylamide treatment followed by TPA promotion also increased the incidence of squamous cell papillomas at the highest dose tested. These results are summarized in Table 5-6. Acrylamide treatment resulted in a significant increase in the combined incidence of bronchiolar adenomas and carcinomas, as indicated in Table 5-7. The data on pulmonary tumors were interpreted with the assumption that TPA does not influence lung tumorigenesis (Bull et al., 1984b).

5.2. MUTAGENICITY

Acrylamide was negative for reverse mutation when tested by plate incorporation at concentration ranges of 0-3.0 and 0-30.0 mg/plate in Salmonella typhimurium strains TA98, TA100, TA1535 or TA1537 with and without metabolic activation by S-9 enzymes (Bull et al., 1984a). An abstract of the work by Lijinsky and Andrews (1980) also reported that acrylamide was not mutagenic in five strains of S. typhimurium. As reviewed in Abe and Sasaki (1982), Shiraishi (1978) reported that acrylamide caused increased aneuploidy and polyploidy, but no increase in SCE, in mouse bone marrow cells in vivo. American Cyanamid Co. (1982), in a brief summary, indicated that acrylamide was negative in the Ames assay and in SCE assay in cultivated Chinese hamster ovary cells with and without metabolic activation and in the micronucleus test in BALB/3T3 mice treated in vivo. Further details were not provided in the summary.

TABLE 5-6

Tumor Initiating Activity of Acrylamide in the Skin of Female Swiss-ICR Mice[a]

Chemical	Dose[b] (mg/kg)	TPA[c]	Cumulative No. of Tumor Bearing Animals[d]	Cumulative No. Tumors/Animal	Histological Classification of Squamous Cell Tumors at Autopsy	
					Papilloma	Carcinoma
Distilled H_2O	0.2 mL	+	0/40 (35)	0	0	0
Acrylamide	75	+	4/40 (34)	0.10	1	1
	150	+	4/40 (32)	0.13	0	3
	300	+	13/40 (32)	0.43	6	4
	300[e]	-	0/40 (36)	0	0	1

[a]Source: Bull et al., 1984b

[b]Dose was administered orally in six divided portions over a 2-week period to the total indicated.

[c]TPA was applied at a dose 2.5 µg/mouse in acetone 3 times/week for 20 weeks beginning 2 weeks after the last dose of initiator.

[d]To be included in the cumulative count a 1 mm mass had to be present in the same location for three consecutive weekly observations. Numbers of animals begun in each group is indicated as the denominator of the ratio. Animals surviving to termination of the experiment at 1 year included in parentheses.

[e]The cumulative number of tumor-bearing animals for the 300 mg/kg dose without TPA was listed as 10/40 in the original publication. M. Robinson (personal communication) indicates that the correct number is 0/40.

TABLE 5-7

Lung Tumor Incidence in ICR-Swiss Mice Treated with Acrylamide[a]

Chemical	Dose[b] (mg/kg)	TPA[c]	N[d]	Alveolor Bronchiolar		Total
				Adenoma	Carcinoma	
Distilled H_2O	0.2 ml	+	36	3	1	4
Acrylamide	75	+	34	6	2	8
	150	+	36	5	1	6
	300	+	34	10	1	11
	300	-	36	4	10	14

[a]Source: Bull et al., 1984b

[b]Dose was administered orally in six divided portions over a 2-week period to the total dose indicated.

[c]TPA was applied at a dose 2.5 µg/mouse in acetone 3 times/week for 20 weeks beginning 2 weeks after the last dose of initiator.

[d]N = No. of animals available for autopsy without unacceptable levels of autolysis. Each group initially contained 40 animals.

5.3. TERATOGENICITY

One group of 12 pregnant Fischer 344 rats were treated by gavage with 20 mg/kg/day of acrylamide in water from day 7-17 of gestation (Agrawal and Squibb, 1981). The method of timing the pregnancy was not reported. Another group of 11 pregnant Fischer 344 rats served as vehicle-dosed controls. One day after birth, ~1/2 of the pups that had been exposed to acrylamide *in utero* were foster-nursed by untreated dams, while the rest of the pups that had been exposed to acrylamide *in utero* remained with acrylamide treated dams. Similarly, the pups that had not been exposed to acrylamide *in utero* were divided into one group that was foster-nursed by acrylamide treated dams and one group that remained with untreated dams. No significant difference in the body weights of the pups was reported at either 2 or 3 weeks after birth. The binding of [^{3}H]-spiroperidol to dopamine receptors in the striatal membranes (in the brain) was significantly decreased in 2-week-old male pups that had been exposed to acrylamide *in utero* regardless of whether they nursed on treated or control dams. The binding of [^{3}H]-spiroperidol to dopamine receptors in the striatal membranes was significantly decreased in 2-week-old female pups that nursed on treated dams regardless of whether or not the female pups had been exposed to acrylamide *in utero*. The results are summarized in Table 5-8. No significant effect on the binding of [^{3}H]-spiroperidol to dopamine receptors in the striatal membranes was reported in any of the 3-week-old pups (Agrawal and Squibb, 1981).

Groups of 20 female Sprague-Dawley rats were treated with 0, 25 or 50 ppm of dietary acrylamide for 2 weeks before mating (Bio/dynamics, Inc., 1979). After mating, the rats were maintained on the 25 or 50 ppm acrylamide diets during 19 days of gestation. Although the rats on the 50 ppm of

TABLE 5-8

Effect of Acrylamide Exposure During Gestation and Nursing on Dopamine Receptor Binding in Rats at 2 Weeks of Age[a]

Treatment Group	Male			Female		
	Body Weight g ± S.E.M.	n	Binding[b]	Body Weight g ± S.E.M.	n	Binding[b]
Control dam with control pups	28.3±1.2	6	34.2±1.8	27.8±1.0	6	26.5±1.3
Control dam with treated pups	25.6±1.1	5	25.1±2.3[c]	25.1±1.5	5	24.1±1.8
Treated dam with control pups	23.8±1.4	5	32.7±2.1	24.1±1.0	5	22.3±1.3[c]
Treated dam with treated pups	24.9±1.3	7	25.2±0.9[c]	25.3±0.9	7	21.5±0.7[c]

[a]Source: Agrawal and Squibb, 1981

[b]Binding values are expressed in pmol of [^{3}H]spiroperidol bound/100 mg protein with standard errors of the mean given.

[c]Differs significantly from corresponding value for untreated rats (Fisher's Least Significant Difference Test $p<0.05$).

dietary acrylamide gained significantly less weight, there were no statistically significant effects from the acrylamide treatment on maternal body weight, maternal mortality, mating or pregnancy rate. The pups displayed no gross malformations at birth and there were no statistically significant differences in litter size, pup weight or viability between controls and groups exposed to acrylamide. At weaning (day 21 of age), four pups from the control group (two males and two females) and eight pups (four males and four females) from each of the treatment groups were examined histologically for neurotoxicity by Spencer and Schaumburg (1977). Four of the pups exposed to acrylamide in utero (dose unspecified) displayed Wallerian degeneration in the tibial nerve, compared with one of the pups from the control group. Three of the pups exposed to acrylamide in utero (dose unspecified) had unilateral optic nerve degeneration; no optic nerve degeneration was observed in the control group. The neurotoxicology report concluded that there was some nerve fiber degeneration in the sciatic and optic nerves of the treated, but not the control, rat pups.

In a series of experiments, Edwards (1976) treated one group of eight pregnant rats (group I) with 200 ppm of dietary acrylamide from the day of mating until the day of parturition; another group of six pregnant rats (group II) with 400 ppm of dietary acrylamide from the day of mating until day 20, at which time the pups were delivered by Caeserian section; and a third group (group III) of four pregnant rats with a single i.v. injection of 100 mg/kg of acrylamide on day 9 of gestation. Control groups of unspecified numbers (except for the control group in experiment II, which had six rats) were reported to have received uncontaminated food or saline injections. At the end of gestation, the pregnant rats in group I had slight gait abnormalities and the pregnant rats in group II had an ataxic

gait. No gross or microscopic malformations or acrylamide effects on litter size were evident. The fetal weight of the pups from group II was significantly less than that of controls, but the pregnant rats in group II that were exposed to dietary acrylamide also consumed significantly less food during gestation. No adverse effects in dams or pups were observed for group III. In a final experiment, Edwards (1976) confirmed the presence of acrylamide in fetal tissue after administering acrylamide to pregnant rats on day 14 or 21 of gestation.

Groups of 17 Fischer 344 rats were treated by gavage with 0 or 20 mg/kg/day of acrylamide on days 6-15 of gestation (Walden et al., 1981). The day of insemination was designated day 0. Immediately after birth, the pups from the acrylamide-treated dams were pooled, as were the pups from the control dams. The pups were then randomly assigned to treated or untreated dams for cross-fostering experiments, in which treated dams nursed control pups, treated dams nursed treated pups, control dams nursed treated pups and control dams nursed control pups. The concentration of intestinal enzymes (alkaline phospatase, citrate synthetase, lactate dehydrogenase, acid phosphatase and β-glucuronidase) was measured in some of the pups 14, 21 and 60 days after birth and in the dams 24 days after parturition. No effect from acrylamide treatment was observed on the level of enzyme activity in the dams. In the pups, however, the level of alkaline phosphatase, acid phosphatase and β-glucuronidase was affected by prenatal and lactational exposure to acrylamide. The level of lactate dehydrogenase activity appeared to be affected only by lactational exposure to acrylamide. No observed effect of acrylamide treatment was reported on the level of citrate synthetase activity (Walden et al., 1981).

5.4. OTHER REPRODUCTIVE EFFECTS

A group of six male ddY strain mice treated twice weekly by gavage with 0.5 mmol/kg (1/3 the LD_{50}, as determined by Hashimoto et al., 1981) for 8 weeks displayed testicular atrophy and a significant decrease in relative testicular weight (Hashimoto et al., 1981). Histologically, there were reduced numbers of spermatozoa, degenerating epithelial cells, especially spermatids and spermatocytes and some multinucleate giant cells. No effect was observed on the Sertoli cells or on the interstitial cells (Hashimoto et al., 1981).

There was a high frequency of chromatid exchanges and breaks in the spermatogonia of ddY mice ingesting 500 ppm of dietary acrylamide for 3 weeks (Shiraishi, 1978). Decreased mitosis in spermatogonia was observed within 24 hours after mice received a single i.p. injection of 50, 100 or 150 mg/kg of acrylamide. Shiraishi (1978) also reported a significant decrease in testis weight.

5.5. CHRONIC TOXICITY

Groups of four male Wistar rats were treated with acrylamide in drinking water at concentrations of 0, 0.73, 1.12, 1.76 or 2.81 mM (0, 52, 80, 125 or 200 mg/l) for 60-90 days (Tanii and Hashimoto, 1983). As indicated in Table 5-9, the body weight of the treated rats was decreased compared with controls but the difference was not significant. The rotarod performance test, however, indicated that the rats treated with 1.76 and 2.81 mM solutions of acrylamide were not able to walk on the rod for longer than 30 seconds. Histological evaluation of the tibial and sural nerves in the high-dose rats revealed moderate to severe morphological changes, shrinkage and loss of myelin fibers, myelin retraction and corrugation of myelin sheaths. In another experiment following the above protocol and described

TABLE 5-9

Effects of Acrylamide Treatment for 90 Days on the Body Weight and Rotarod Performance in Rats[a]

Concentration[b] (mM)	Body Weight (% of control)	Rotarod Performance[c] (number of animals)
0	100 ± 7	0
0.73	96 ± 9	0
1.12	96 ± 3	0
1.76	92 ± 6	3
2.8	90 ± 12	4

[a]Source: Tanii and Hashimoto, 1983

[b]Test solutions were given as drinking water and prepared freshly at least once/day

[c]The number of animals whose mean walking time on the rod was <30 seconds, half the maximum.

in the same report, the binding of [^{3}H]-colchicine to neurotubulin in the sciatic nerve was decreased in rats treated at 2.81 mM acrylamide (Tanii and Hashimoto, 1983).

In a subchronic study, groups of 10 female and 23-29 male Fischer 344 rats were given 0, 0.05, 0.2, 1.0, 5.0 or 20.0 mg/kg/day of acrylamide in the drinking water for 92-93 days (Burek et al., 1980). After the 90-day treatment period was completed, a preselected group of male rats from each exposure level was given tap water for up to 144 days to determine the reversibility of the effects. The remaining rats were killed at the end of the treatment period. Body weight gain was significantly decreased in males and females at 20 mg/kg/day. The relative weights of brain, heart, liver and kidney were increased while the relative weight of thymus (females) and testicles were decreased in males and females at 20 mg/kg/day. Males at 5 mg/kg/day had increased relative liver weights and females at 20 mg/kg/day. Females at 20 mg/kg/day had decreased serum cholinesterase activity and increased serum alkaline phosphatase activity. Treatment-related hematologic changes consisted of significant decreases in packed cell volume, total erythrocyte counts and hemoglobin concentrations in males and females at 20 mg/kg/day and in females at 5 mg/kg/day. Male and female rats at 20 mg/kg/day had significant increases in landing foot spread measurement and displayed curling of toes, splaying of rear limbs, incoordination and posterior weakness. Treatment-related gross alterations occurred only in 20 mg/kg/day males and females and consisted of perineal soiling, decreased adipose tissue, decreased liver size, darkened kidneys, mottled lungs, testicular and uterine atrophy, atrophy of skeletal muscle, distention of the urinary bladder and thickening of the stomach. Histologic changes (electron microscopy examinations) were observed in peripheral nerves (axon and myelin degeneration) of rats at $\geq$5 mg/kg/day and in the spinal cord of

20 mg/kg/day rats. Electron microscopy also revealed ultrastructural alterations in peripheral nerves of male rats treated with 20, 5 or 1 mg/kg/day of acrylamide. Nerve tissue from female rats was not examined with the electron microscope. No adverse effects were reported at dose levels of 0.05 or 0.2 mg/kg/day of acrylamide. The ultrastructural alterations in peripheral nerve tissue, described in rats treated with 1 mg/kg/day of acrylamide for ~90 days, were reversed 25 days after the rats resumed drinking uncontaminated water. The adverse changes reported in rats treated with 5 mg/kg/day of acrylamide were no longer apparent 111 days after the rats resumed drinking water uncontaminated with acrylamide; in rats treated with 20 mg/kg/day the adverse effects were no longer apparent after 144 days of recovery (Burek et al., 1980).

As reported in Section 5.1., groups of 90 male and 90 female CDF Fischer 344 rats were exposed to 0, 0.01, 0.1, 0.5 or 2.0 mg/kg/day of acrylamide in their drinking water for 738-746 days (Dow, 1984). Evaluation of hematological (packed cell volume, hemoglobin, total erythrocytes, leukocyte count, platelet count and red cell indices) and clinical chemistry (blood urea nitrogen, total protein, albumin, globulin, glucose, alkaline phosphatase, glutamic-pyruvic transaminase, and cholesterol levels) parameters, as well as urinalysis, revealed no effects from acrylamide treatment. The body weight of male rats imbibing 2.0 mg/kg/day of acrylamide was significantly less than the body weight of control rats, beginning ~90 days after initiation of treatment and continuing throughout the rest of the experiment. Although the body weight of male rats imbibing 0.5 mg/kg/day and of female rats imbibing 2.0 mg/kg/day was less than that of control rats, the decrease was not statistically significant. The relative and absolute liver weight was increased in both male and female rats imbibing 2.0 mg/kg/day of acrylamide, but statistical analysis of the increase was not reported.

There were multifocal areas of altered hepatocytes in the rats treated with acrylamide, while the control rats had single areas of altered hepatocytes (not further described). After ~20 months of treatment, there was a significantly increased mortality rate for both male and female rats treated with 2.0 mg/kg/day of acrylamide; at approximately the same time, an increased incidence of various tumors was observed. Therefore, the increased mortality rate may have been associated with the increased tumor incidence, but the Dow (1984) study did not address this point and the cause of death in each animal that died before the termination of the experiment was not reported. There was focal degeneration of individual axons and myelin sheaths in the tibial nerve of male and female rats treated with 2.0 mg/kg/day of acrylamide. The degeneration was demonstrable histologically, but not clinically. Other differences between control and treated groups of rats were not considered biologically significant by Dow (1984) because they were sporadic, represented a decreased incidence of a pathological lesion, were changes secondary to tumor-related changes or were within the expected incidence range for control rats (Dow, 1984).

Groups of 10 male Fischer 344 rats were treated by gavage 3 days/week with 0, 5, 10 or 20 mg/kg/day of acrylamide for 13 weeks (Tilson et al., 1979). An additional group of 10 male Fischer 344 rats was handled but not gavaged. Behavioral tests of hindlimb extensor response, spontaneous motor activity and forelimb grip strength were performed after 1, 4, 7, 10 and 13 weeks of acrylamide exposure. Within 3 days of the last acrylamide treatment, all (n=10) of the rats in the 10 mg/kg/day dose group, 50% (n=5) of the rats in the 20 mg/kg/day dose group and 50% (n=5) of the rats in the control group were killed, and the sciatic nerve and medulla oblongata evaluated histologically for neurotoxicity. Five weeks after the last

acrylamide treatment, the remaining five rats in the control group and the 20 mg/kg/day dose group were killed and evaluated histologically for neurotoxicity. Rats receiving 20 mg/kg/day of acrylamide had significantly decreased body weights (weeks 7-13), significantly decreased hindlimb extensor response (weeks 7-13) and spontaneous motor activity (weeks 10-13) and nerve fiber degeneration at the end of 13 weeks. At the end of the 5-week recovery period, the body weight, the hindlimb extensor response and spontaneous motor activity of the rats that had received 20 mg/kg/day was no longer significantly different from the controls, but histologic evidence of neurotoxicity was still evident in the acrylamide treated rats, as indicated in Table 5-10. The only significant difference in forelimb grip strength between the acrylamide treated (20 mg/kg/day) rats and the control rats was seen 1 week after the last acrylamide treatment. No significant neurobehavioral differences between controls and rats treated at 10 mg/kg/day were reported. Neuropathological effects were observed in the rats treated at 10 mg/kg/day at the end of the treatment period but not at the end of the recovery period, as indicated in Table 5-10.

Groups of 10 male and 10 female 8- to 9-week-old Dow-Wistar rats were treated for 90 days with 0, 3, 9, 30, 70, 90, 110, 300 or 400 ppm of dietary acrylamide, equivalent to 0, 0.3, 0.9, 3.0, 7.0, 9.0, 11.0, 30.0 and 40.0 mg/kg/day, respectively, as reported by McCollister et al. (1964). No adverse effects on the rats appearance, behavior, growth, mortality, organ weights or histology were reported. No adverse effects were observed after extending the treatment of rats with 70-110 ppm of dietary acrylamide from 90-189 days. Although hindleg weakness was observed in one male rat exposed to 90 ppm of dietary acrylamide and in several male and female rats exposed to 300 ppm of dietary acrylamide, no histopathology in the brain or spinal

TABLE 5-10

The Neuropathological Effects of Acrylamide Given Subchronically to Rats[a]

Group	Number of Animals Rated		
	Neuropathology		
	None	Slight[b]	Moderate[c]/Severe[d]
After 13 weeks of Dosing:			
Controls	5	0	0
Acrylamide - 10 mg/kg	0	9	1
Acrylamide - 20 mg/kg	0	0	5
5 Weeks after Cessation of Dosing:			
Controls	5	0	0
Acrylamide - 20 mg/kg	0	0	5

[a]Source: Tilson et al., 1979

[b]Slight damage = signs of early fiber degeneration

[c]Moderate damage = presence of Schwann cell columns

[d]Severe damage = regenerating or remyelinating fibers in the presence of fiber degeneration

cord was reported. Mortality was increased in the rats treated with 300 ppm of dietary acrylamide; all of the males and six of the females died by day 42 of treatment. The effect of 400 ppm of dietary acrylamide was so severe that it was discontinued after 25 days of treatment.

In a study by Fullerton and Barnes (1966), which was reviewed in NIOSH (1976), an unspecified number of male albino rats were treated for 48 weeks with 0, 100, 200, 300 or 400 ppm of dietary acrylamide, equivalent to 0, 6-9, 10-14, 15-18 or 20-30 mg/kg/day, respectively. Slight leg weakness was observed in the rats treated with 400, 300, 200 and 100 ppm of dietary acrylamide after 3, 4, 12 and 40 weeks, respectively. Severe leg weakness developed in all groups except the control group and the group of rats exposed to 100 ppm of dietary acrylamide. Microscopic degeneration of peripheral nerves was reported in all of the rats demonstrating signs of clinical neurotoxicity; however, no histopathology was observed in the kidney, spleen, pancreas, adrenal, lung, brain or spinal cord (Fullerton and Barnes, 1966).

Groups of two cats were treated 5 days/week for 1 year with acrylamide in the diet at equivalent dosages of 0.03, 0.1, 0.3, 1, 3, or 10 mg/kg/day (McCollister et al., 1964). Cats receiving 10 mg/kg/day developed hindleg weakness by day 26 and were unable to stand by day 52. The cats receiving 3 mg/kg/day developed hindleg weakness by day 68, although some hindleg muscle twitching first became apparent 26 days after treatment began. Only one of the two cats receiving 1 mg/kg/day displayed any neurotoxicity, as indicated by hindleg twitching 26 days after treatment began and signs of hindleg stretching when walking 240 days after the start of treatment. Although 5 of the 6 cats in the groups receiving 0.03, 0.1 or 0.3 mg/kg/day died from causes reported not to be associated with acrylamide treatment by 106 days

after the start of the experiment, no toxic effects were observed in the one remaining cat for the duration of the study. Histopathological evaluation of the brain and spinal cord revealed no effects from acrylamide treatment (McCollister et al., 1964).

Two cats were treated with 3 mg/kg/day of acrylamide administered in their drinking water for 252 or 294 days (Schaumburg et al., 1974). Gait disorders were first observed 70 and 163 days after the start of treatment. Distal muscle weakness and dropfoot in the hindlimbs was observed by the seventh month. Nerve fiber degeneration and reduced numbers of myelinated fibers were observed during histological evaluation after completion of treatment. In addition, the muscle fibers were vacuolated and shrunken with irregular borders, indicating muscle degeneration subsequent to denervation (Schaumburg et al., 1974).

As reviewed by NIOSH (1976), no observed effects were reported in six female rats given 10 mg/kg/day of acrylamide orally, 5 times/week for ~5 months (Hamblin, 1956).

As reviewed in NIOSH (1976), four baboons (Papio hamadryas) were treated with 10 mg/kg/day of dietary acrylamide for 89-137 days and one baboon was treated with 15 mg/kg/day for 94 days (Hopkins, 1970). The baboons treated with 10 mg/kg/day developed the first signs of incoordination and hindlimb weakness between days 42 and 82 of treatment and the first signs of forelimb weakness between days 61 and 96 of treatment. Wallerian degeneration and a reduction in the number of myelinated fibers were observed upon histological examination of nervous tissue from one baboon treated with 10 mg/kg/day for 118 days and biopsied after a 19-day recovery period. The baboon treated with 15 mg/kg/day of acrylamide developed the first signs of incoordination and hindlimb weakness on day 42 of treatment and the first signs of forelimb

weakness on day 73 of treatment. In a subsequent report on the Hopkins (1970) study, a decrease in the action potentials for both nerve and muscle fibers in baboons treated with 10 or 15 mg/kg/day was observed (Hopkins and Gilliatt, 1971).

Doses of 3 and 10 mg/kg/day of acrylamide were administered by gavage to one monkey each, 5 days/week for 1 year (McCollister et al., 1964). Mild hindleg weakness was observed after 48 days and severe muscle weakness after 69 days in the monkey treated with 10 mg/kg/day of acrylamide. The acrylamide treatment was stopped and the monkey recovered in 54 days. Sporadic deficits in reflex reactions (knee jerk reflex, pupillary reflex), but no weight loss, were observed in the monkey treated with 3 mg/kg/day of acrylamide. Histological examination of the liver, kidney, brain and spinal cord after 1 year of treatment at 3 mg/kg/day resulted in no observed adverse effects. No adverse effects were observed in monkeys that received 1 (n=1), 0.3 (n=2), 0.1 (n=1), 0.03 (n=1) or 0 (n=2) mg/kg/day of acrylamide administered in bananas 5 days/week for 1 year. The parameters evaluated were growth, general appearance, behavior, periodic neurological examinations, liver and kidney weights, gross pathology and histopathology (McCollister et al., 1964).

Four female adult pigtail monkeys (Macaca nemistrina) were treated orally with 10 mg/kg/day of acrylamide 5 days/week until overt toxic signs, such as loss of balance, decreased activity, hindlimb weakness and forelimb tremor were observed at the time indicated in Table 5-11 (Maurissen et al., 1983). In addition, two monkeys served as controls. Vibratory sense and pickup time, but not electrical sensitivity, were adversely affected during the treatment in all four monkeys. Three of the four treated monkeys had

TABLE 5-11

Oral Administration of Acrylamide to Monkeys[a]

Monkey Number	Dosing Period (days)	Total Cumulative Dose (mg/kg)
M-946	61	450[b]
M-947	52	380
M-948	44	320
M-949	61	450
M-944	68	0[c]
M-945	68	0

[a]Source: Maurissen et al., 1983

[b]Acrylamide 10 mg/kg daily, 5 days/week

[c]Sham dosing

significant weight loss. Nerve biopsies (examined with the electron microscope) from two of the treated monkeys during a period of observed alteration in their vibratory sense demonstrated that there were changes in myelin morphology (such as invagination, disruption or loss). Maurissen et al. (1983) attributed the altered morphology observed in peripheral nerves to acrylamide treatment, although the ultrastructure of control nerve fibers were not examined.

Other studies in which monkeys were exposed to acrylamide by the oral route reported that signs of neurotoxicity, indicated by hindlimb or forelimb weakness, were observed before the monkeys had received 13 weeks of acrylamide treatment (Leswing and Ribelin, 1969; Hopkins, 1970; Merigan et al., 1982). The doses that were given in these experiments ranged from 16-20 mg/kg/day and were administered 5 days/week.

5.6. OTHER RELEVANT INFORMATION

An oral LD_{50} was reported to be between 150 and 180 mg/kg/day for rats (Dow, 1984). In a more detailed report, Tilson and Cabe (1979) reported that the oral LD_{50} for rats was between 203 and 300 mg/kg at 24 hours after treatment, but between 159 and 191 mg/kg at 168 hours after treatment.

The effects of acrylamide exposure have been extensively studied in rats. Neurotoxicity, as measured by fore- and hindlimb weakness (Tilson and Cabe, 1979; Anderson, 1983; Lapin et al., 1984; Boyes, 1981), by degenerative changes in peripheral nerves (Suzuki and Pfaff, 1973; Anderson, 1983), by alterations in axonal transport (Kemplay and Cavanaugh, 1983; Jakobsen and Sidenius, 1983; Miller et al., 1983), by changes in dopamine or serotonin binding affinities within the CNS (Rafales et al., 1982, 1983; Ali et al., 1983; Agrawal et al., 1981; Bondy et al., 1981) and by effects observed on Purkinje cells (Cavanagh and Nolan, 1982; Cavanagh and Gysbers, 1983) is

a well-documented effect of acrylamide exposure in rats. In addition to its effect on brain glutathione-S-transferase, acrylamide has also been reported to affect hepatic glutathione-S-transferase (Dixit et al., 1981; Das et al., 1982; Srivastava et al., 1983, 1984). Body weight loss has often been observed in short-term studies of acrylamide exposure in rats (Agrawal et al., 1981; Rafales et al., 1983; Tilson and Cabe, 1979). Loeb and Anderson (1981) reported that vitamin B_6 supplementation delayed the onset and reduced the severity of neurotoxicity in acrylamide treated rats. An earlier report by Kaplan et al. (1973) indicated that dietary deficiencies in pyridoxine or thiamine did not affect the severity or onset of acrylamide induced neurotoxicity in rats, but that pretreatment with microsomal enzyme inducers increased the amount of acrylamide required to produce neurologic deficits in rats.

Mice treated with 250 ppm of acrylamide in the drinking water for 12 or 19 days developed adverse neurobehavioral lesions, as measured by rotarod performance and landing foot-spread (Gilbert and Maurissen, 1982). The mice in the Gilbert and Maurissen (1982) study had decreased body weights after acrylamide exposure. In addition to body weight loss and neurotoxicity, as indicated by loss of hindlimb strength, mice exposed to acrylamide by i.p. injections were reported to increase their milk-licking activity (Teal and Evans, 1982; Evans and Dempster, 1984; Evans and Teal, 1981). Cutaneous application of acrylamide in mice resulted in reduced levels of glutathione, glutathione-S-transferase and aryl hydrocarbon hydroxylase activity in murine skin and liver (Mukhtar et al., 1981).

Peripheral neuropathy has been described in beagles (Thomann et al., 1974) and greyhounds (Satchell et al., 1982). In addition, greyhounds treated acutely with acrylamide developed megaesophagus (Satchell et al., 1982; Satchell and McLeod, 1981, 1984), a disorder indicative of deterioration of vagal afferents, and altered baroreceptor reflex responses from the carotid sinus (Satchell, 1984).

As reviewed by Howland (1981), acrylamide treatment in cats results in peripheral nerve damage (Prineas, 1969; Schaumburg et al., 1974), motor and sensory deficits (Lowndes and Baker, 1976; Lowndes et al., 1978a,b), as well as CNS damage (Ghetti et al., 1973; Prineas, 1969; Spencer and Schaumburg, 1977; Kuperman, 1958). Focal degeneration accompanied by increased relative concentrations of phospholipids in peripheral nerves was described in cats treated intramuscularly with acrylamide for 10 days (Howland and Lowndes, 1984).

Several reviews of the effects of acrylamide in humans (Tilson, 1981; NIOSH, 1976; ACGIH, 1980) indicate that neurotoxicity occurs in humans as evidenced by paresthesias in the fingers, coldness, tenderness to the touch, numbness in the lower limbs accompanied or followed by weakness of the hands and feet (Auld and Bedwell, 1967; Garland and Patterson, 1967; Igisu et al., 1975; Kesson et al., 1977; Takahashi et al., 1971).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute lethal effects of acrylamide have been examined in three species of freshwater fish. Using the harlequin fish (Rasbora heteromorpha) as the test species, Tooby et al. (1975) reported flowthrough 24-, 48- and 96-hour LC_{10} and LC_{50} values. The respective LC_{10} values were 390, 220 and 103 mg/ℓ while LC_{50} values were 460, 250 and 130 mg acrylamide/ℓ, respectively, for 24-, 48- and 96-hour exposures. The static 24- and 96-hour LC_{50} values determined using goldfish (Carassius auratus) were 460 and 160 mg/ℓ, respectively (Bridie et al., 1979b). Experiments of 14 days duration were conducted by Hermens and Leeuwangh (1982) using guppies (Poecilia reticulata) as the test species. The 14-day LC_{50} value was 490 µmol/ℓ (34.8 mg/ℓ).

6.2. CHRONIC EFFECTS

Based on acute toxicity data, Tooby et al. (1975) extrapolated and reported a 3-month LC_{50} of 10 mg acrylamide/ℓ for the harlequin fish.

Using two sewage works and a river as in situ test systems, Brown et al. (1982) indicated that levels of acrylamide at ~40 µg/ℓ severely decrease the faunal composition in the water, which may prevent re-establishment of populations for up to 8 weeks. The effect of acrylamide at this level over the period of study was not appraised, but no obvious fish kills resulted.

6.3. PLANT EFFECTS

Pertinent data regarding the toxic effects of acrylamide to aquatic plant species were not located in the available literature cited in the Appendix.

6.4. RESIDUES

Brown et al. (1982) indicated that acrylamide was somewhat persistent in aquatic systems, even in water treatment facilities. During a 48-hour period ~50% was lost in sewage treatment plants. The majority of the loss resulted from microbial degradation of acrylamide. Acrylamide placed in a study river was quite persistent and was detected throughout the water column and estuary; there was no loss from adsorption or degradation.

6.5. OTHER RELEVANT INFORMATION

In an English abstract of a Russian study (Isuev and Chernyshov, 1975), acrylamide was reported to copolymerize with lipids in eggs of the Caspian sturgeon (Acipenser stellatus). Exposures at 0.004 mg acrylamide/ℓ for 3 hours caused the copolymerization and accumulation of acrylamide in the eggs. Blastula and gastrula stage embryos had the highest acrylamide content. Details regarding the toxicity or lethality of acrylamide to the embryos were not available.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The ACGIH (1983) has adopted a TWA-TLV of 0.3 mg/m³ and a STEL of 0.6 mg/m³ for overall exposure to acrylamide by the cutaneous route, including mucous membranes and eyes. Exposure may occur either by direct contact or by air-borne contamination. Based on a NOEL of 0.3-1 mg/kg/day of dietary acrylamide in cats (McCollister et al., 1964), the ACGIH (1980) recommended that workers absorb $\leq$0.05 mg/kg/day of acrylamide. Therefore, assuming a daily breathing volume of 10 m³/day in the workplace, a TWA-TLV of 0.3 mg/m³ was recommended.

NIOSH (1976) has recommended and the Occupational Safety and Health Administration (OSHA) has adopted a standard for acrylamide exposure of 0.3 mg/m³ for an 8-hour TWA (CFR, 1981).

An ADI of 0.11 mg/day of acrylamide was reported by the U.S. EPA (1984a). The ADI was derived from the TLV with a caution that recent evidence indicated that acrylamide may be carcinogenic.

The FDA (1972) has recommended that residual acrylamide monomer not exceed 0.05% concentration in beet and cane sugar juice.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of acrylamide were not located in the available literature cited in the Appendix.

8. RISK ASSESSMENT

Acrylamide was carcinogenic to rats when administered in the drinking water at dosages of 0.01, 0.1 0.5 or 2.0 mg/kg/day, resulting in significantly increased incidences of mammary, CNS, thyroid follicular, uterine and scrotal tumors at 2.0 mg/kg/day (Dow, 1984) (see Table 5-1). Acrylamide was positive as a tumor initiator in Sencar mice and Swiss mice treated orally or intraperitoneally at ≤50 mg/kg/day, 3 days/week for 2 weeks, followed by dermal application of the tumor promotor, TPA (Bull et al., 1984a,b). Acrylamide was also positive in the lung adenoma assay when administered to A/J mice orally or intraperitoneally at doses ≤25 mg/kg/day, 3 days/week for 8 weeks (Bull et al., 1984a).

Acrylamide was negative for reverse mutation in at least five strains of S. typhimurium with and without metabolic activation (Bull et al., 1984a; Lijinsky and Andrews, 1980; American Cyanamid Co., 1982) and negative for SCE in mouse bone marrow cells and hamster ovary cells and in the micronucleus test in mice (Shiraishi, 1978; American Cyanamid Co., 1982). Although acrylamide does not appear to be teratogenic or to cause increased resorptions or abortions in rats treated at oral doses ≤20 mg/kg/day during gestation (Agrawal and Squibb, 1981; Bio/dynamics, Inc., 1979; Edwards, 1976; Walden et al., 1981), nerve degeneration (Bio/dynamics, Inc., 1979), transient decrease in striatal dopamine receptors (Agrawal and Squibb, 1981), reduced birth weight (Edwards, 1976) and altered intestinal enzyme activity were reported in the offspring of rats that had been treated with acrylamide at ≤20 mg/kg/day during gestation. An adverse effect on testicular morphology in mice treated by gavage at 0.5 mmol/kg/day (~36 mg/kg/day), 2 days/week for 8 weeks was reported by Hashimoto et al. (1981), but no

functional evaluation was performed. As indicated in Sections 5.5. and 5.6., there is extensive evidence documenting the neurotoxicity of acrylamide in rats, mice, cats, dogs, monkeys and humans. Neurological effects on both the peripheral and CNS, often accompanied by body weight loss, appeared to be the primary effect of acrylamide exposure. In the subchronic and chronic studies in animals (Tanii and Hashimoto, 1983; Burek et al., 1980; Dow, 1984; Tilson et al., 1979; McCollister et al., 1964; Schaumburg et al., 1974; Hopkins, 1970; Hopkins and Gilliatt, 1971; Fullerton and Barnes, 1966; Leswing and Ribelin, 1969; Merigan et al., 1982), acrylamide was administered in drinking water at dosages $\leq$20 mg/kg/day for 90 days to 2 years, by gavage at $\leq$20 mg/kg/day for 3 or 5 days/week for 90 days to 1 year, or in the diet at dosages $\leq$40 mg/kg/day for up to 1 year. From these studies it appears that 1 mg/kg/day is the LOAEL, at which there was microscopic evidence of damage to peripheral nerves of rats treated with acrylamide in drinking water for ~90 days (Burek et al., 1980). A dose of 0.5 mg/kg/day in rats treated with acrylamide in the drinking water for ~2 years (Dow, 1984) is the highest NOEL. Since acrylamide has been demonstrated to be carcinogenic, however, it is appropriate to derive a q_1^*.

The data reported by Dow (1984) provided tumor incidence data in rats (see Table 5-1) that can be used for deriving a q_1^*. The q_1^* was calculated using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (Federal Register, 1980). The animal q_1^* was converted to its human equivalent by multiplying the animal q_1^* by the cube root of the ratio of human to animal body weights and by the cube of the ratio of the lifespan of the experimental animals to the duration of the experiment, in this case 1. The human body weight was assumed to be 70 kg; the animal body weight was experimentally determined to be 0.4 kg for male

rats and 0.25 kg for female rats. A summary of the q_1^* values for humans is presented in Table 8-1. The data used to calculated the individual q_1^* values are presented in Tables 8-2 to 8-7.

It is not possible to calculate pooled incidence data for the sites which showed significant increases since the Dow report (1984) did not provide data on individual animals and it is likely that some of the animals presented more than one tumor type. The highest q_1^* value for an individual site is 2.3 $(mg/kg/day)^{-1}$ calculated based on combined mammary adenomas, fibromas, adenocarcinomas and fibroadenomas in female rats. From the Dow data it is not clear which, if any, of the animals may have shown both benign and malignant mammary tumors. Therefore, combining these incidence rates may slightly overestimate risk for this site. However, this is presented as an interim estimate pending the availability and analysis of the raw data from this study.

TABLE 8-1

Summary of Human q_1^* Values for Tumors from Different Sites of Origin in Fischer 344 Rats After Chronic Exposure to Acrylamide

Site of Tumor	Sex	Tumor Type	q_1^* $(mg/kg/day)^{-1}$
Mammary gland	female	adenoma, fibroma, fibroadenoma, adenocarcinoma	2.27
Scrotum	male	mesothelioma	8.92×10^{-1}
Thyroid gland	male	adenoma	5.00×10^{-1}
CNS	female	glioma, astrocytoma	5.23×10^{-1}
Thyroid	female	papillary adenoma adenocarcinoma	4.59×10^{-1}
Uterus	female	adenocarcinoma	2.87×10^{-1}

TABLE B-2

Cancer Data Sheet for Derivation of q_1^*

Compound: Acrylamide

Reference: Dow, 1984

Species, Strain, Sex: rat/Fischer 344/female

Body weight: 0.25 kg (measured)

Length of exposure (le) = 738-746 days

Length of experiment (Le) = 738-746 days

Lifespan of animal (L) = 738-746 days

Tumor site and type: mammary gland/adenoma, fibroadenoma, fibroma, adenocarcinoma

Route, vehicle: oral/drinking water

Experimental Doses or Exposures (mg/kg/day)*	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	12/60
0.01	0.01	12/60
0.1	0.1	10/60
0.5	0.5	21/58
2.0	2.0	29/61

Unadjusted q_1^* from study = 3.55000×10^{-1} $(mg/kg/day)^{-1}$

Human q_1^* = 2.27924 $(mg/kg/day)^{-1}$

TABLE 8-3

Cancer Data Sheet for Derivation of q_1^*

Compound: Acrylamide

Reference: Dow, 1984

Species, Strain, Sex: rat/Fischer 344/male

Body weight: 0.4 kg (measured)

Length of exposure (le) = 738-746 days

Length of experiment (Le) = 738-746 days

Lifespan of animal (L) = 738-746 days

Tumor site and type: scrotum/mesothelioma

Route, vehicle: oral/drinking water

Experimental Doses or Exposures (mg/kg/day)*	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	3/60
0.01	0.01	0/60
0.1	0.1	7/60
0.5	0.5	11/60
2.0	2.0	10/60

Unadjusted q_1^* from study = 1.5954841×10^{-1} $(mg/kg/day)^{-1}$

Human q_1^* = 8.9242523×10^{-1} $(mg/kg/day)^{-1}$

TABLE B-4

Cancer Data Sheet for Derivation of q_1^*

Compound: Acrylamide

Reference: Dow, 1984

Species, Strain, Sex: rat/Fischer 344/female

Body weight: 0.25 kg (measured)

Length of exposure (le) = 738-746 days

Length of experiment (Le) = 738-746 days

Lifespan of animal (L) = 738-746 days

Tumor site and type: thyroid gland/adenocarcinoma, papillary adenoma

Route, vehicle: oral/drinking water

Experimental Doses or Exposures (mg/kg/day)*	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	1/58
0.01	0.01	0/59
0.1	0.1	1/59
0.5	0.5	1/58
2.0	2.0	5/60

Unadjusted q_1^* from study = 7.0135572×10^{-3} $(mg/kg/day)^{-1}$

Human q_1^* = 4.5883621×10^{-3} $(mg/kg/day)^{-1}$

TABLE 8-5

Cancer Data Sheet for Derivation of q_1^*

Compound: Acrylamide

Reference: Dow, 1984

Species, Strain, Sex: rat/Fischer 344/female

Body weight: 0.25 kg (measured)

Length of exposure (le) = 738-746 days

Length of experiment (Le) = 738-746 days

Lifespan of animal (L) = 738-746 days

Tumor site and type: CNS/astrocytoma and glioma

Route, vehicle: oral/drinking water

Experimental Doses or Exposures (mg/kg/day)*	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	1/60
0.01	0.01	2/60
0.1	0.1	1/60
0.5	0.5	1/60
2.0	2.0	9/61

Unadjusted q_1^* from study = 7.9874118×10^{-2} $(mg/kg/day)^{-1}$

Human q_1^* = 5.2254708×10^{-1} $(mg/kg/day)^{-1}$

TABLE 8-6

Cancer Data Sheet for Derivation of q_1^*

Compound: Acrylamide

Reference: Dow, 1984

Species, Strain, Sex: rat/Fischer 344/male

Body weight: 0.4 kg (measured)

Length of exposure (le) = 738-746 days

Length of experiment (Le) = 738-746 days

Lifespan of animal (L) = 738-746 days

Tumor site and type: thyroid gland/adenoma

Route, vehicle: oral/drinking water

Experimental Doses or Exposures (mg/kg/day)*	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	1/60
0.01	0.01	0/58
0.1	0.1	2/59
0.5	0.5	1/59
2.0	2.0	7/59

Unadjusted q_1^* from study = 8.953834×10^{-2} $(mg/kg/day)^{-1}$

Human q_1^* = 5.0082776×10^{-1} $(mg/kg/day)^{-1}$

TABLE 8-7

Cancer Data Sheet for Derivation of q_1^*

Compound: Acrylamide

Reference: Dow, 1984

Species, Strain, Sex: rat/Fischer 344/female

Body weight: 0.25 kg (measured)

Length of exposure (le) = 738-746 days

Length of experiment (Le) = 738-746 days

Lifespan of animal (L) = 738-746 days

Tumor site and type: uterus/adenocarcinoma

Route, vehicle: oral/drinking water

Experimental Doses or Exposures (mg/kg/day)*	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	1/60
0.01	0.01	2/60
0.1	0.1	1/60
0.5	0.5	0/59
2.0	2.0	5/60

Unadjusted q_1^* from study = 4.39211×10^{-2} $(mg/kg/day)^{-1}$

Human q_1^* = 2.8733766×10^{-1} $(mg/kg/day)^{-1}$

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

As indicated in Table 9-1, the main effects of chronic or subchronic exposure to acrylamide are fetotoxicity (Bio/dynamics, Inc., 1979), decreased body weight (Dow, 1984), shortened lifespan (Dow, 1984) and neurotoxicity (Maurissen et al., 1983; Schaumburg et al., 1974; Burek et al., 1980). Although many other studies that document these effects were also discussed in Chapter 5, the studies listed in Table 9-1 generated the data from which the lowest human MED could be derived for each effect. The human MED was derived by multiplying the animal dose in mg/kg/day by the cube root of the ratio of the animal to human body weight and multiplying by 70 kg, the assumed weight of a human. Table 9-1 also lists the RV_d, the RV_e, the CS (the product of the RV_d and the RV_e) and the appropriate RQ for each human MED reported.

Fetotoxicity, as evidenced by altered intestinal enzyme levels (Walden et al., 1981), decreased birth weight (Edwards, 1976), histologically demonstrable nerve degeneration (Bio/dynamics, Inc., 1979) and changes in dopamine receptors in the brain (Agrawal and Squibb, 1981), was reported when pregnant rats were treated with acrylamide by gavage or in the food. The nerve degeneration described in pups after the dams had been treated with 25 or 50 ppm of dietary acrylamide during pregnancy and for 2 weeks before mating (Bio/dynamics, Inc., 1979) occurred at the lowest dose evaluated for fetotoxic effects. Because the Bio/dynamics, Inc. (1979) report does not distinguish between the effects seen at 25 and 50 ppm of dietary acrylamide, the lower dose was used to derive the human MED. The body weight of a rat was assumed to be 0.35 kg in the derivation of the human MED.

TABLE 9-1

Composite Scores for Acrylamide

Species	Animal Dose/ Exposure	Human MED (mg/kg/day)	RV_d	Effects	RV_e	CS	UF	Reference
Monkey	10 mg/kg/day for 10 weeks	257.9	1.9	histologically demonstrable nerve degeneration accompanied by vibratory sense loss	7	13.3	1000	Maurissen et al., 1983
Cat	3 mg/kg/day for 252-294 days	75.9	2.7	histologically demonstrable nerve degeneration accompanied by hind-weakness	7	18.9	1000	Schaumburg et al., 1974
Rat	2 mg/kg/day for 2 years	21.4	3.5	increased mortality in males and females after ~20 months of treatment; histologic evidence of nerve degeneration; decreased body weight in males and increased liver weight in males and females	10	35	100	Dow, 1984
Rat	25 ppm in diet during gestation (1.25 mg/kg/day)	15.0	3.7	fetotoxicity as evidenced by nerve degeneration; no signs of maternal toxicity	8	29.6	100	Bio/dynamics, Inc., 1979
Rat	1 mg/kg/day for 90 days	12.0	3.9	histological demonstration of nerve degeneration, but clinical pathology was not always observed	6	23.4	100	Burek et al., 1980

Neurotoxicity is the most widely documented effect of acrylamide exposure. Neurotoxicity has been reported after subchronic exposure in the cat and monkey, and after chronic exposure in the rat, as indicated on Table 9-1. Although the Maurissen et al. (1983) study is only 10 weeks in duration, it was included because treatment was stopped after clinical signs became apparent in the monkeys treated at 10 mg/kg/day. In another study (Hopkins, 1970), baboons were treated with 10 mg/kg/day of acrylamide for 89-137 days. The neurotoxic effects of acrylamide did not regress with continued exposure. Therefore, if Maurissen et al. (1983) had continued to dose the pigtail monkeys for an additional 3 weeks, it is doubtful that results different from those obtained after 10 weeks of dosing would have been obtained. Histological examination of peripheral nerves from pigtail monkeys with vibratory sense loss indicated that myelin was altered, disrupted or lost. The weight of a monkey was assumed to be 3.5 kg. The baboon study of Hopkins (1970) provides a higher human MED, despite an effect seen at the same dose level of 10 mg/kg/day. This higher MED resulted because baboons have higher body weights than macaque monkeys; therefore, it was not used. No uncertainty factor was used because similar endpoints were observed in rats treated chronically.

In the experiment of Schaumburg et al. (1974), two cats, treated with 3 mg/kg/day of acrylamide for 252 and 294 days developed hindleg weakness. Histological evaluation revealed nerve fiber degeneration. The body weight of a cat was assumed to be 3.3 kg in the derivation of the human MED.

The chronic toxicity study by Dow (1984) reported that there was increased degeneration of peripheral nerves, demonstrable histologically but not clinically, in rats treated for 2 years with 2 mg/kg/day of acrylamide, but not with 0.5 mg/kg/day of acrylamide. In a subchronic toxicity study

(Burek et al., 1980), however, ultrastructural alterations were reported in peripheral nerves of rats treated with 1 mg/kg/day of acrylamide, but not in the peripheral nerves of rats treated with 0.2 mg/kg/day of acrylamide, the next lowest dose tested. Therefore, the lowest dose capable of causing neurotoxicity in Fischer 344 rats appears to be ~1 mg/kg/day. The animal dose of 1 mg/kg/day was multiplied by the cube root of the ratio of the assumed average body weight of rats (0.35 kg) to the human body weight (assumed to be 70 kg), to derive the human MED indicated on Table 9-1. No uncertainty factor was used because the same endpoint was observed in the chronic study at 2.0 mg/kg/day, but not at 0.5 mg/kg/day. The corresponding RV_d is 3.9. The RV_e is 6 and the CS, a product of the RV_d and RV_e, is 23.4, which corresponds to an RQ of 100.

Shortened lifespan was observed in the chronic (Dow, 1984), but not the subchronic (Burek et al., 1980) rat study because increased mortality rates did not occur until after 20 months of 2 mg/kg/day of acrylamide treatment. In the Dow (1984) study, both males and females had decreased survival. Because the experimentally determined average body weight of the female rats was 0.25 kg, this value was used in deriving the human MED reported in Table 9-1.

As can be seen from Table 9-1, the highest CS is obtained from the Dow (1984) study in which increased mortality was seen in male and female rats; therefore, it is the basis for the recommended RQ of 100 (Table 9-2). An RQ of 100 is supported by the Bio/dynamics, Inc. (1979) study in which feto-toxicity was reported and by the Burek et al. (1980) study in which neuro-toxicity is reported.

TABLE 9-2

Acrylamide

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral, in drinking water
Dose*:	21.4 mg/day
Effect:	increased mortality
Reference:	Dow, 1984
RV_d:	3.5
RV_e:	10
Composite Score:	35
RQ:	100

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*Equivalent human dose

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR (F=1/ED_{10}) FOR CARCINOGENICITY

The data available on the carcinogenicity of acrylamide were presented in Section 5.1. and Table 5-1. In the Dow (1984) study, rats were treated with 0, 0.01, 0.1, 0.5 or 2.0 mg/kg/day of acrylamide administered in the drinking water for 2 years. The female rats treated with 2.0 mg/kg/day of acrylamide had significantly increased incidences of mammary tumors, CNS tumors, thyroid follicular tumors, uterine tumors and malignant tumors from all sites. The male rats treated with 2.0 mg/kg/day of acrylamide had significantly increased incidences of scrotal mesotheliomas, thyroid follicular tumors and malignant tumors from all sites. In the Bull et al. (1984a,b) studies, mice were treated orally with 0, 6.25, 12.5, 25.0 or 50.0 mg/kg/day of acrylamide for 2 or 8 weeks and were intraperitoneally administered 0, 1, 3, 10, 30 or 60 mg/kg of acrylamide 3 times/week for 8 weeks. The mice were observed for up to 1 year after the start of the treatment. A dose-related increase in the incidence of pulmonary adenomas was observed in males and females after 1 year. Application of a tumor promoter to the backs of female mice treated orally with acrylamide resulted in an increased incidence of squamous cell carcinoma and papilloma in females. Cutaneous application of acrylamide followed by application of a tumor promotor also resulted in an increased incidence of squamous cell carcinoma and papilloma. Although the Bull et al. (1984a,b) studies are of short exposure durations, they are less suitable for derivation of a q_1^* or F factor; they do support the evidence provided by the Dow (1984) study.

The data used to derive unadjusted 1/ED values and F factors are presented in Table 9-3. The F values for several cases were not calculated because the computation of the upper confidence limits on extra risk for the ED_{10} is omitted if the ED_{10} is greater than the largest experimental

TABLE 9-3

Derivation of Potency Factor (F)
Agent: Acrylamide

Reference:	Dow, 1984				
Exposure route:	oral				
Species:	rat				
Strain:	Fisher 344				
Sex:	female				
Vehicle or physical state:	drinking water				
Body weight*:	0.25 kg				
Duration of treatment:	738-746 days				
Duration of study:	738-746 days				
Lifespan of animal:	738-746 days				
Target organ:	mammary gland	CNS	thyroid gland	uterus	all sites
Tumor type:	adenoma, fibroma, adenofibroma	glioma/astrocytoma	adenoma/adeno-carcinoma	adenocarcinoma	malignant
Experimental doses/ exposure: (mg/kg/day:	0, 0.01, 0.1, 0.5, 2.0	0, 0.01, 0.1, 0.5, 2.0	0, 0.01, 0.1, 0.5, 2.0	0, 0.01, 0.1, 0.5, 2.0	0, 0.01, 0.1, 5.0, 2.0
Transformed doses (mg/kg/day):	0, 0.01, 0.1, 0.5, 2.0	0, 0.01, 0.1, 0.5, 2.0	0, 0.01, 0.1, 0.5, 2.0	0, 0.01, 0.1, 0.5, 2.0	0, 0.01, 0.1, 5.0, 2.0
Tumor incidence:	10/60, 11/60, 9/60 19/58, 23/61	1/60, 2/60, 1/60, 1/60, 9/61	1/58, 0/59, 1/59, 1/58, 5/60	1/60, 2/60, 1/60, 0/59, 5/60	23/60, 23/60, 16/60, 24/60, 40/60
Unadjusted $1/ED_{10}$:	1.5432865	0.535415	not calculated (see text)	not calculated (see text)	1.2531967
$1/ED_{10}$ (F factor):	10.096385	3.5027526	not calculated (see text)	not calculated (see text)	8.1985793

TABLE 9-3 (cont.)

Reference:	Dow, 1984		
Exposure route:	oral		
Species:	rat		
Strain:	Fisher 344		
Sex:	male		
Vehicle or physical state:	drinking water		
Body weight[a]:	0.4 kg		
Duration of treatment:	738-746 days		
Duration of study:	738-746 days		
Lifespan of animal:	738-746 days		
Target organ:	scrotum	thyroid gland	all sites
Tumor type:	mesothelioma	adenoma	malignant
Experimental doses/ exposure: (mg/kg/day):	0, 0.01, 0.1, 0.5, 2.0	0, 0.01, 0.1, 0.5, 2.0	0, 0.01, 0.1, 0.5, 2.0
Transformed doses (mg/kg/day):	0, 0.01, 0.1, 0.5, 2.0	0, 0.01, 0.1, 0.5, 2.0	0, 0.01, 0.1, 0.5, 2.0
Tumor incidence:	3/60, 6/60, 7/60, 11/60, 18/60	1/60, 0/58, 2/59, 1/59, 7/59	31/60, 26/60, 29/60, 36/60, 43/60
Unadjusted $1/ID_{10}$:	0.8367697	0.5077035	3.0772317
$1/ID_{10}$ (f factor):	4.6804269	2.8398114	17.212326

[a]reported

dose (Crump and Watson, 1979). The unadjusted $1/ED_{10}$ value was corrected for interspecies extrapolation by multiplying by the cube root of the ratio of human to animal weight and by the cube of the ratio of the duration of the study to the lifespan of the experimental animals, which is 1 in the Dow (1984) study. Human body weight is assumed to be 70 kg, while the male rat body weight was experimentally determined to be 0.4 kg and the female rat body weight was experimentally determined to be 0.25 kg. The highest F factor value (17.2) was obtained from the data for the incidence of all malignant tumors in male rats and is recommended for the carcinogenicity hazard ranking of acrylamide.

There is sufficient evidence to classify acrylamide as an experimental animal carcinogen because it is carcinogenic in rats and mice when administered orally or intraperitoneally or when applied topically and followed by application of a tumor promotor. There is inadequate evidence to classify acrylamide as a human carcinogen. Therefore, based on the IARC (1979) methodology for qualitatively assessing potential carcinogens, acrylamide can be placed in IARC group 2B. Because the F factor of 17.2 falls between 10 and 100, acrylamide can be placed in Potency Group 2. A Potency Group 2 and an IARC Group 2B chemical has a Medium Hazard Ranking according to the Scheme for Reportable Quantities under CERCLA. Under the U.S. EPA (1984b) proposed guidelines, acrylamide would be classified in category B2, a probable human carcinogen. This category is used when there is inadequate evidence for carcinogenicity from human studies, but adequate evidence from animal studies.

Acrylamide

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in January, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

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Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. p. 2878.

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Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

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U.S. EPA. 1984. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

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Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Int., Fish Wildl. Ser. Resource Publ. 137. Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California. State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. U.S. EPA, Office Pesticide Programs, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

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